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The usefulness of symptoms alone or combined for general practitioners in considering the diagnosis of a brain tumour: a case-control study using the clinical practice research database (CPRD) (2000-2014)

Mio Ozawa,[1] Paul M Brennan,[2] Karolis Zienius,[2] Kathreena M Kurian,[1] William Hollingworth,[1] David Weller,[3] Robin Grant,[4] Willie Hamilton,[5] Yoav Ben-Shlomo[1]

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For numbered affiliations see end of article.

Correspondence to
Professor Yoav Ben-Shlomo;
Y.Ben-Shlomo@bristol.ac.uk

ABSTRACT

Objectives To evaluate the utility of different symptoms, alone or combined, presented to primary care for an adult brain tumour diagnosis.

Design and setting Matched case-control study, using the data from Clinical Practice Research Datalink (2000–2014) from primary care consultations in the UK.

Method All presentations within 6 months of the index diagnosis date (cases) or equivalent (controls) were coded into 32 symptom groups. Sensitivity, specificity, positive predictive values (PPVs) and positive likelihood ratios were calculated for symptoms and combinations of symptoms with headache and cognitive features. Diagnostic odds ratios were calculated using conditional logistic regression, adjusted for age group, sex and Charlson comorbidity. Stratified analyses were performed for age group, sex and whether the tumour was of primary or secondary origin.

Results We included 8,184 cases and 28,110 controls. Seizure had the highest PPV of 1.6% (95% CI 1.4% to 1.7%) followed by weakness 1.5% (1.3 to 1.7) and confusion 1.4% (1.3 to 1.5). Combining headache with other symptoms increased the PPV. For example, headache plus combined cognitive symptoms PPV 7.2% (6.0 to 8.6); plus weakness 4.4% (3.2 to 6.2), compared with headache alone PPV 0.1%. The diagnostic ORs were generally larger for patients <70 years; this was most marked for confusion, seizure and visual symptoms.

Conclusion We found seizure, weakness and confusion had relatively higher predictive values than many other symptoms. Headache on its own was a weak predictor but this was enhanced when combined with other symptoms especially in younger patients. Clinicians need to actively search for other neurological symptoms such as cognitive problems.

Strengths and limitations of this study

- Largest study to examine systematically a wide range of symptoms for patients with both primary and secondary brain tumours in primary care.
- Greater power has enabled us to look into symptom combinations both acutely and within a 6-month window, as well as stratifying by age group and gender.
- Results only apply to patients presenting in primary care and are not generalisable to all brain tumours as we have not included patients who first present to the emergency department.
- For some symptoms and combinations of symptoms we had to aggregate symptom groups to increase statistical power.
- We can only examine what symptoms were coded by general practitioners rather than what symptoms were actually discussed during the consultation and any clinical signs that were elicited.

INTRODUCTION

Primary brain tumours are rare, so for every 100 000 individuals one would only expect between to around 25 new cases in a year.[1 2] A primary care practitioner working in a practice of around 10 000 patients would expect to diagnose between two to three patients with a brain tumour every year. Other more common cancers can metastasise to the brain, with similar symptoms[1]; patients may or may not have had the primary cancer previously diagnosed. Even where one exists, the doctor may not immediately make a connection depending on the length of the past cancer history and its pathological type. There is a very wide range of possible presenting symptoms depending on the location and size of the tumour and whether it is primary or secondary. Symptoms may be general

non-specific rather than focal neurological and may or may not suggest the correct diagnosis.

General practitioners can find it difficult to distinguish which patients should be referred for rapid assessment because of a suspicion of a brain tumour based on symptoms alone, rather than through a less acute diagnostic pathway. Additionally, patients may present for the first time directly as an emergency to hospital, often with a seizure or acute weakness (paralysis), thereby bypassing primary care altogether.[3] Some of these patients will have previously consulted with their general practitioner with non-specific symptoms possibly related to their brain tumour.

A previous descriptive study examining patients' symptoms presenting in primary care listed the most common presentations and their predictive values.[4] A systematic review of cancer of the brain and central nervous system identified six studies with 159 938 patients.[5] However, only two of these six studies examined adult brain tumours, with one study being a case cohort study of headache with follow-up to determine the risk of being subsequently diagnosed as a brain tumour.[6] In the case control study, the seven most common features associated with brain tumours were (in order of increasing positive predictive values (PPV)): motor loss (0.026%), visual disorder (0.035%), memory loss (0.036%), headache (0.09%), generalised weakness (0.14%), confusion (0.20%) and new onset seizure (1.2%). There was some evidence that predictive values were greater for patients aged 60 to 69 years.[4] The case cohort study found a slightly higher risk of a brain tumour for headache, with the PPV in that study ranging from 0.08% to 0.28% below and above 50 years of age, suggesting that older age may be more predictive.[6]

We have previously reported, using data from the National Audit of Cancer diagnosis in Primary Care, that patients presenting with headaches, behavioural/cognitive changes or other/non-specific symptoms attended their general practitioner (GP) more frequently before referral. Isolated headache and memory loss were associated with a much slower diagnostic pathway, mainly due to delay in referral to a specialist.[7] A mathematical model of tumour growth suggests that delay to the start of radiotherapy has a possible deleterious effect on patient survival in patients with glioblastoma, the most aggressive type of tumour.[8] However, there is almost no evidence for this in one observational study[9] and more aggressive tumours may present more rapidly due to sudden onset of severe symptoms and in turn have worse survival.

In this paper, we re-examine the diagnostic utilities of a wide range of symptoms for patients who present with brain tumours, compared with a control population, in a primary care setting across the UK. We specifically focussed on whether combinations of features for headache and cognitive symptoms can improve diagnosis, whether the predictive value of clinical features differ by sex, age sub-groups and whether the diagnosis was a primary or secondary tumour.

MATERIAL AND METHODS

Study design and selection of cases and controls

We used electronic patient record data from the UK's Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database. CPRD contains anonymised primary care medical records from around 680 UK general practices, representing 8.8% of the entire UK population (https://www.cprd.com/).

These data comprise information routinely recorded by GPs during their consultations with patients. Personal information is collected, as well as clinical events such as symptoms, diagnoses, prescriptions, treatment and death. Information is stored using Read codes – the standard clinical terminology within UK primary care.[10]

Cases were defined as patients aged 18 and over with a record of either a primary or secondary brain tumour, diagnosed between 1st January 2000 and 31st December 2014. We excluded meningiomas because of their difference in prognosis and presentation. We defined cases of brain tumours by using a large number of relevant Read codes mapped to the CPRD medcodes (see online supplementary appendix I for the complete list). The index date of diagnosis was then taken as the earliest date with one of these specific brain tumour codes in the CPRD files.

We used a matched case-control study design so that controls were matched to cases where possible by year of birth, sex and practice and had the same index date allocated as their respective case. To enhance power, we used a 1:4 case to control ratio. Patients had to come from a practice with at least 6 months of up-to-standard data before a diagnosis. We excluded any cases and controls, who had no GP visit for 6 months prior to the index date to remove 'ghost' patients.

Symptoms

We created symptom dictionaries based on a dual top down and bottom up approach using clinical knowledge of phenomenology for the former and frequency of symptom presentations in the tumour case series for the latter. We used the first four digits of the Read codes to identify potential symptoms related to a tumour and then one of our clinical researchers (KZ), classified these into appropriate symptom groups, as the Read code system allows the same phenomenology to be coded in more than one way. Symptoms were grouped according to similarity (such as smell and taste). All the symptom groups were then checked again by several other members of the team, including an academic general practitioner and clinical epidemiologist (YBS, WHa, MO). This procedure is in line with best practice for generating code lists using electronic health records.[11]

In some cases, we aggregated individual symptoms into larger groups due to small numbers (which would have produced very imprecise estimates) as long as this made clinical sense. For example the broad category of visual symptoms included diplopia, loss of vision, deteriorating vision, patient concerned about eyesight, has a squint, other binocular vision disorders, etc. This generated 32

independent symptom groups of which 23 were neurologically-related symptoms (see online supplementary appendix II). To examine consistency, we compared our Read codes for some symptom groups (eg, weight loss, vomiting, etc) with those previously derived from another cancer diagnostic study (led by WHa)[12] to check for completeness and, if necessary, appended any additional codes that we had missed very occasionally.

As our previous work[7] had already highlighted the diagnostic delays with headache and cognitive problems, we examined the utility of these symptoms in combination with other symptoms. For these analyses, we aggregated the original cognition variable with presentations labelled 'concentration' and 'confusion' to create a broader 'cognitive' variable to enhance our statistical power to look at other combinations. We looked at combinations of symptoms that appeared together with headache and cognitive complaints acutely within 1 month or that appeared to be independent temporally but may have been related to the same underlying cause that is, brain tumour, within a 6-month time window prior to the index date (see below for further details about the different time window cut-offs that we tried initially). We called these combinations as headache or cognitive 'plus' group if the patient had either headache or cognitive problems with another neurological-related symptom(s). If the patient did not have any other neurological related symptoms, we treated them as 'headache only' or 'cognitive only'.

Other covariates

We also derived the Charlson Index Score[13] as other comorbidities may be used by clinicians to explain the presence or absence of some symptoms, which may result in diagnostic confusion and delay in diagnosis. Alternatively, a prior history of a non-brain tumour cancer may lower a doctor's threshold for suspicion that a headache may relate to metastatic disease. The Charlson Index is constructed by identifying 17 categories of comorbid disease. Each disease is based on their association with 1 year all-cause mortality to produce a total prognostic score. We only used comorbidities prior to the index date for cases (and equivalent date for controls) so that cases could have a Charlson Score of zero.

Statistical analyses

Our aim was to derive the diagnostic utilities of specific symptoms or combination of symptoms for patients who presented to general practice that is, the diagnostic odds ratio (OR) of having a brain tumour conditional on seeking care. We adjusted for sex and age in 10 year age-bands as having excluded 'ghost patients' there were some imbalances between cases and controls. We produced basic descriptive data using summary statistics and regression or X^2 tests. We calculated diagnostic utilities (sensitivity, specificity, positive predictive values (PPV) and positive likelihood ratio (PLR) which is defined as sensitivity/1-specificity, or the frequency of symptoms in cases divided by frequency of symptoms in controls. We initially looked at a variety of different latency periods prior to the index date: 1 month, 3 months, 6 months and 1 year, as we were not certain of the optimum retrospective time-period to evaluate.

Because of our sampling strategy (four controls to one case), the crude PPV from the two by two table will be grossly overestimated as we have only taken a small random sample of all potential controls and hence our incidence of brain tumours is artefactually elevated, by design, at 20%. We therefore weighted the control samples by the actual denominator in CPRD data set in each combination of age (less than 40, 40 to 49, 50 to 59, 60 to 69, 70 to 79, 80 and over) and sex categories. Cases have a default weight of 1 as we took all cases rather than a sample. To test for the strength of association between symptoms and case/control status and to produce a single summary indicator, we used conditional logistic regression and computed diagnostic ORs (DORs),[14] 95% CIs and p values after adjustment for gender, age group and Charlson Index. Stata 15 was used for the analysis.

We repeated our analyses using sex and age strata (<60, 60 to 69, ≥70 years), as in a previous publication,[4] to examine for possible heterogeneity of associations. To examine whether clinical presentation profiles differed by pathology, we also undertook a subgroup analysis stratifying the tumours into primary and secondary and tested for heterogeneity between the DORs by symptoms using multinomial logistic regression.

Patient and public involvement

No patients were involved in the design, analysis or reporting of this work. However, carers of patients attended a meeting where preliminary results were presented and provided helpful comments on our findings.

RESULTS

In total 8184 cases and 28 110 controls were included in our study after excluding 98 cases (1.2%) and 5240 controls (18.6%) without a GP visit 6 months prior to the diagnosis date. This comprised of 4454 (54.4%) primary malignant brain tumours and 3730 (45.6%) secondary brain tumours. The age and gender distribution for cases and controls are shown in table 1 and was very similar due to the matching process. Cases showed higher Charlson Index Score than controls.

Table 2 shows the frequency of symptoms in cases and controls in the 6 months before diagnosis. We chose this time-period rather than 1 year as the increase in frequency of symptoms was far greater for controls (approximately doubling) than cases over this period. This highlights the temporal clustering of symptoms in the 6 months prior to diagnosis rather than a simple linear increase due to the longer observation period. Six months compared with 3 months had greater sensitivity, so was also considered to be more useful and is consistent with the natural history of primary brain tumours,[15] though our sample also includes secondary tumours.

Table 1 Sociodemographic characteristics in cases and controls

	Brain tumour status	
	Case	Control
	(n=8184) (%)	(n=28 110) (%)
Gender		
Male	4113 (50.3)	13 257 (47.2)
Female	4071 (49.7)	14 853 (52.8)
Total	8184 (100)	28 110 (100)
Age at the event		
18–39	462 (5.7)	1375 (4.9)
40–49	687 (8.4)	2084 (7.4)
50–59	1438 (17.6)	4639 (16.5)
60–69	2326 (28.4)	8123 (28.9)
70–79	2148 (26.3)	7812 (27.8)
>80	1123 (13.7)	4077 (14.5)
Total	8184 (100)	28 110 (100)
Charlson index score		
0	3045 (37.2)	16 530 (58.8)
1	1253 (15.3)	5194 (18.5)
2	1753 (21.4)	3083 (11.0)
3	850 (10.4)	1402 (5.00)
4+	1283 (15.7)	1901 (6.8)
Total	8184 (100)	28 110 (100)

We found that 23 of the 32 symptom groups differed between cases and controls (only these are shown in table 2). The most sensitive neurological symptom groups for cases were headache and ataxia (gait-related) symptoms, though non-neurological symptoms included fatigue and cough, perhaps reflecting an underlying different primary malignancy. The three least specific symptoms (highest false-positive rate) were cough, depression and fatigue. From a diagnostic perspective however, the largest positive predictive values (>1.0%) and PLRs were seen for seizure, followed by weakness and confusion, but even then their predictive values ranged from 1.4% to 1.6%, highlighting that the vast majority of patients with these features will transpire not to have a brain tumour.

Both headache and cognitive symptoms were predictive but with more modest effects, so that headache, though the most sensitive feature only had a PPV of 0.2% (ie, brain tumour found in 2 per 1000 patients with this symptom). Further exploration of these symptoms showed that the diagnostic utilities were enhanced when looking at the headache/cognitive plus groups (table 3) as compared with headache or cognitive only symptoms. While symptom combinations were more predictive when presenting together within a month, the predictive values were only slightly larger than when the longer time window of 6 months was taken. The two strongest combination of symptom combinations were headache plus the broader range of cognitive symptoms (PPV 7.2%) and cognitive plus weakness (PPV 9.6%).

The results from our conditional logistic models found that for most tumour-related symptoms, there were no sex differences, but depression, fatigue, seizure and headache were more diagnostically useful in men (male and female DORs depression 2.77 vs 1.87, p value for effect modification=0.004; fatigue 6.37 vs 4.61, p value for effect modification=0.004; seizure 59.4 vs 27.0, p value for effect modification=0.02; headache only 7.08 vs 4.88, p value for effect modification=0.006) while sleep disturbance was a stronger predictor in women (1.54 vs 2.38, p value for effect modification=0.007). When we stratified the sample into three age groups (<60, 60 to 69, ≥70 years), we found evidence of differences in the predictive value of some symptoms by age group (see table 4). In all cases, other than for depression, symptoms among patients younger than 70 years showed greater diagnostic ORs. This pattern was particularly marked for confusion, where the largest DOR was seen in the 60 to 69 year age group, and for seizure andvisual symptoms where patients <70 years had much higher DORs than older patients though for visual symptoms this was driven by the <60 year age group.

Our multinomial logistic models found that some symptoms were equally predictive for both primary and secondary tumours (eg, headache DOR 21.2 and 21.5 for primary and secondary tumours, respectively), cognitive symptoms were more common for primary tumours (DOR 17.6 vs 6.8 for primary and secondary tumours, respectively, p value for heterogeneity <0.001) and generalised symptoms such as lack of appetite were more common in secondary tumours (DOR 3.6 vs 9.0 for primary and secondary tumours respectively, p value for heterogeneity <0.001).

DISCUSSION

We have examined the value of clinical presentations in primary care to aid the clinician in suspecting the diagnosis of a brain tumour. Like previous studies,[4 5 7] we find the obvious clinical features such as seizures, weakness and other cognitive problems were the most predictive findings. However, the data make it clear that no feature alone is very predictive in absolute terms. The vast majority of patients with such features do not have a brain tumour (false-positive) though they may have another important pathology. In addition, we note that several non-specific symptoms, such as cough, fatigue and appetite problems are also more common and this is most likely related to our inclusion of secondary brain tumours, that are normally excluded from such studies. Interestingly, while headache was equally predictive for both primary and secondary tumours, the broader category of cognitive symptoms were more predictive for primary tumours, which we speculate might reflect the infiltrative nature and location of gliomas[16] compared

Table 2 Frequency of symptoms that differed between cases and controls in 6 months before diagnosis

	Brain tumour status					
	Case (n=8184)		Control (n=28 110)			
	Number with symptoms	Sensitivity	Number with symptoms	Specificity	PPV* (%)	PLR* (95% CI)
Anxiety	360	(4.4)	458	(98.4)	0.1	2.06 (1.86 to 2.28)
Appetite	125	(1.5)	72	(99.7)	0.3	8.40 (7.06 to 10.0)
Ataxia	624	(7.6)	351	(98.8)	0.4	9.42 (8.74 to 10.2)
Cognition	323	(3.9)	99	(99.6)	0.7	18.4 (16.5 to 20.4)
Concentration	11	(0.1)	3	(100.0)	0.2	4.49 (2.49 to 8.12)
Confusion	474	(5.8)	92	(99.7)	1.4	36.9 (33.8 to 40.3)
Consciousness	148	(1.8)	112	(99.6)	0.3	6.79 (5.79 to 7.95)
Cough	852	(10.4)	2010	(92.8)	0.1	1.73 (1.62 to 1.84)
Depression	438	(5.4)	699	(97.5)	0.1	1.84 (1.68 to 2.01)
Dizziness	310	(3.8)	219	(99.2)	0.2	5.93 (2.53 to 6.61)
Falls	318	(3.9)	343	(98.8)	0.2	5.73 (5.15 to 6.37)
Fatigue	1005	(12.3)	699	(97.5)	0.2	5.72 (5.40 to 6.06)
Headache	1163	(14.2)	518	(98.2)	0.2	5.70 (5.40 to 6.01)
Nausea	604	(7.4)	353	(98.7)	0.2	6.22 (5.77 to 6.72)
Pain	305	(3.7)	531	(98.1)	0.1	2.51 (2.25 to 2.80)
Seizure	489	(6.0)	46	(99.8)	1.6	40.8 (37.5 to 44.5)
Sensation	252	(3.1)	190	(99.3)	0.2	5.11 (4.53 to 5.76)
Sleep	286	(3.5)	466	(98.3)	0.1	2.70 (2.41 to 3.03)
Speech	382	(4.7)	87	(99.7)	0.8	19.7 (17.9 to 21.8)
Vertigo	84	(1.0)	100	(99.6)	0.1	3.66 (2.96 to 4.53)
Visual	327	(4.0)	163	(99.4)	0.5	12.3 (11.1 to 13.7)
Weakness	303	(3.7)	37	(99.9)	1.5	39.4 (35.3 to 43.9)
Weight	161	(2.0)	163	(99.4)	0.2	3.94 (3.38 to 4.60)

*Calculated after weighting for population sampling.
PLR, positive likelihood ratio; PPV, positive predictive value.

with metastatic disease,[17] though it is not obvious why this may be the case.

We explored whether combinations of symptom presentation would enhance predictive value for two common, but non-specific presentations of headache and cognitive complaints. They did indeed enhance prediction but with the expected cost of lower sensitivity. In particular, we think the concept of 'headache plus and cognitive plus' is useful as evidenced by the better PPV and PLRs. Symptoms that occurred closely together (within 1 month) had stronger predictive value but widening the time window to 6 months was only a little weaker and captures more cases.

Simple demographic factors are also helpful in raising clinical suspicion. For example, headaches in men were more predictive than in women and younger age (<70 years) was in general associated with higher predictive values for most features except depression, presumably because with increasing age there is an increase in other comorbid conditions[18] providing alternative reasons for the symptoms.

Strengths and limitations

This is the largest study so far to examine systematically a wide range of symptoms for patients with both primary and secondary brain tumours as this more realistically reflects the clinical dilemma facing GPs. While the data come from the UK, they are likely to be generalisable to other high income primary care settings. We excluded meningiomas as most are detected asymptomatically in imaging for other indications, tend to be more benign and slow growing with a more insidious development of clinical symptoms. Our greater power has enabled us to look into symptom combinations both acutely and within a 6-month window, as well as stratifying by age group and gender. However, several important limitations remain. It is important that these results only apply to patients presenting in primary care and are not generalisable to

Table 3 Frequency of symptom combinations for headache and cognitive features in 1 or 6 months before diagnosis

	Brain tumour status					
	Case (n=8184)		Control (n=28 110)			
	Number with symptoms	Sensitivity	Number with symptoms	Specificity	PPV††(%)	PLR (95% CI)
Headache						
Headache plus (1 month)	476	(5.8)	81	(99.7)	0.7	18.1 (16.6 to 19.8)
Headache only (1 month)	687	(8.4)	437	(98.4)	0.1	3.92 (3.65 to 4.21)
Headache plus (6 months)	569	(7.0)	116	(99.6)	0.6	16.3 (15.0 to 17.6)
Headache only (6 months)	594	(7.3)	402	(98.6)	0.1	3.57 (3.30 to 3.86)
Headache +depression (6 months)	83	(1.0)	32	(99.9)	0.4	9.90 (7.99 to 12.3)
Headache +cognition (6 months)	47	(0.6)	2	(100.0)	5.9	165 (123 to 221)
Headache +weakness (6 months)	35	(0.4)	1	(100.0)	4.4	122 (87 to 171)
Headache +nausea (6 months)	167	(2.0)	11	(100.0)	2.0	55 (47 to 64)
Cognitive*						
Cognitive plus (1 month)	325	(4.0)	48	(99.8)	1.5	39 (35 to 44)
Cognitive only (1 month)	435	(5.3)	140	(99.5)	0.7	18.9 (17.2 to 20.7)
Cognitive plus (6 months)	379	(4.6)	69	(99.8)	1.2	32.0 (29.0 to 35.3)
Cognitive only (6 months)	381	(4.7)	119	(99.6)	0.7	19.6 (17.8 to 21.7)
Cognitive +depression (6 months)	62	(0.8)	20	(99.9)	0.5	12.9 (10.1 to 16.6)
Cognitive +headache (6 months)	111	(1.4)	4	(100.0)	7.2	205 (169 to 249)
Cognitive +weakness (6 months)	19	(0.2)	1	(100.0)	9.6	282 (176 to 451)
Cognitive +nausea (6 months)	60	(0.7)	5	(100.0)	3.5	96 (74 to 124)

*This cognitive variable is a composite of cognition, concentration and confusion symptoms.
† Calculated after weighting for population sampling.
PLR, positive likelihood ratio; PPV, positive predictive value.

all brain tumours as we have not included patients who first present to the emergency department. While we have a larger number of tumours, for some symptoms and for the combination of symptoms we had to aggregate symptom groups to increase our numbers. Even then some of our estimates are imprecise due to small numbers, especially in the control sample. We can only examine what symptoms were coded by GPs rather than what symptoms were actually discussed during the consultation. For example, hardly any patients had early morning headache recorded. It may be that GPs did not ask about this specific feature or they did, but it was absent, hence not coded, or they did but they simply coded it as a generic headache rather than use the specific early morning headache code.[19] Similarly, a GP may have elicited several symptoms but only chose to code some, probably the most worrying feature where they suspect serious pathology and there is evidence that for haematuria, jaundice and abdominal pain 38% of these feature were missing from Read codes but hidden in free text.[20] If combinations of features are less likely to be coded and occur more frequently in case than controls, then this sort of misclassification would result in an underestimation of the value of combined features. We did not try to look at data on clinical examination as this is known to be under-recorded in this setting.[4] We undertook many hypothesis tests including tests for interaction so one should be cautious over some of the 'statistically significant' results, especially within the 0.01 to 0.05 range as these may simply reflect a type I chance error.

We believe that this work has the following implications. To enhance the chance of earlier suspicion and hence referral of patients with possible brain tumours, GPs must actively question patients about other neurological related symptoms that may not emerge from the initial presenting history especially for headache and cognitive presentations (headache and cognitive plus). Referral threshold should be lower where there is a past history of malignancy as almost half of our cases were secondary tumours. Non-specific cancer-related features, such as

Table 4 Diagnostic Odds Ratios* for individual clinical presentations stratified by age group (<60, 60 to 69, ≥70 years) that showed evidence of effect modification

Symptom	Diagnostic ORs: Age group (years) <60	60–69	≥70	P value for effect modification
Anxiety	1.44	1.39	1.24	0.02
Ataxia	8.28	9.57	5.16	0.004
Confusion	43.9	96.4	12.6	<0.001
Consciousness	6.93	7.03	3.1	0.02
Depression	1.5	2.65	2.77	<0.001
Headache	11.3	9.15	6.08	<0.001
Nausea	6.86	5.82	3.19	<0.001
Seizure	89.3	70	14.5	<0.001
Sleep	2.72	1.48	1.78	0.03
Visual	22.8	5.11	4.9	<0.001

*Models adjusted for age group, gender and Charlson Comorbidity Index.

lack of appetite, may also be helpful even when there is no known past history. There is a need to review any past consultations in the last 1 to 6 months, that may not initially have been considered to be temporally related, for symptom combinations that might suggest a common pathological cause rather than assuming multiple pathologies are present (this principle is known as Occam's razor). Symptoms in younger patients may have greater significance, though one must be careful in assuming that symptoms in older patients are always due to comorbidities. Recent qualitative research highlights that patients often experience multiple subtle changes ('you weren't quite yourself', 'brain not working properly') that may be more noticed by a partner.[21]

Despite all the above, diagnostic information will result in many false-positive referrals, highlighting the need for better methods to help GPs screen possible referrals. We have recently demonstrated that a simple semantic verbal fluency task, that is, name as many animals as possible within a minute, is helpful in differentiating patients with headache and a brain tumour from those with headache, but without a brain tumour, presumably because of subtle cognitive deficits that the patient and/or carer may not have noticed (Zienius *et al* personal communication). Other options to support assessment of brain tumour risk could include biomarkers, either from blood, saliva or breath.[22] These have the potential to eventually be done rapidly, assuming they are not overly expensive. Future research should examine the addition of such tests either in primary care and the emergency department to enhance diagnostic utility with the ultimate aim of producing an automated diagnostic algorithm that would enable better risk stratification of patients that need urgent assessment.

In conclusion, we have shown how difficult it is to for GPs to accurately suspect brain tumours and if referral is based solely on the presence or absence of the various symptoms reported in this study then the majority of patients will turn out not to have a brain tumour. The predictive value of headache and cognitive symptoms can be enhanced by considering a wider array of symptoms ('headache or cognitive plus') in the 6 months prior to diagnosis and as well as the age of the patient. Newer tests are required to help GPs enhance their diagnostic abilities.

Author affiliations
[1]Population Health Sciences, University of Bristol, Bristol, UK
[2]Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK
[3]General Practice, University of Edinburgh, Edinburgh, UK
[4]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[5]Primary Care Diagnostics, University of Exeter Medical School, Exeter, UK

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